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I hereby certify that the paper or, if this paper is a transmittal letter, every other paper or fee referred to therein is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents & Trademarks, Washington, DC 20231, on November 21, 1997 (Date of Deposit)

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Date

Nadine Jean
Name

File No. ~~1010/16959-US4~~

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): WEINER *et al.*

Serial No.: 08/469,492 Group Art Unit: 1818

Filed: June 6, 1995 Examiner: Duffy, P.

For: **BYSTANDER SUPPRESSION OF AUTOIMMUNE DISEASES**

November 18, 1997

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

DECLARATION OF MALCOLM FLETCHER UNDER 37 C.F.R. § 1.132

I, Malcolm Fletcher, declare and state as follows:

1. I have been the Vice President of Clinical and Regulatory Affairs at AutoImmune Inc., the owner of U.S. Application Ser. No: 08/469,492 (the '492 application), since November of 1992. From 1991 to 1992, I was Medical Director at Cato Research, Ltd.. From 1980 to 1990, I was employed by Burroughs Wellcome, Inc., the last eight years as Medical Director for its Canadian operations. I trained in Medicine at the Medical College of St. Bartholomew's Hospital, University of London, becoming a

Licentiate of the Royal College of Physicians and a Member of the Royal College of Surgeons in 1972. In 1975 I received a D.A. from the Royal College of Surgeons.

2. In connection with my employment at AutoImmune Inc., I have overseen the clinical testing of pharmaceuticals that are based on the oral administration of autoantigens for the therapeutic treatment of T cell-mediated autoimmune disease, particularly in humans. A pharmaceutical composition of AutoImmune Inc. that has been the subject of much clinical study is "Myloral", a product made from bovine myelin, which contains myelin basic protein. Myloral has been orally administered to patients suffering from multiple sclerosis.

3. I am advised by AutoImmune's patent counsel that the Examiner in charge of the '492 application has based the rejection of the claims in this application in part on a report of Phase III Myloral trials (reported in *BioWorld Today*, 8(77): 1,3). I am also advised that the Examiner has interpreted the Phase III trial results as showing that myelin administration is ineffective for treating multiple sclerosis in humans. In my opinion, however, these results by no means demonstrate that Myloral is ineffective and, furthermore, although not sufficient for FDA approval, the results are encouraging as to the efficacy of Myloral.

4. During my employment at AutoImmune Inc., an ongoing study of

Myloral was conducted in a limited number of patients. 17 patients from a proof of principal trial experienced an average 75% reduction in attack rate during their first year of treatment over the prior rate of attacks, and maintained lower average attack rates with continuing therapy. Some of these patients took Myloral for as long as six years.

5. The "Phase III" study relied on by the Examiner was conducted over a two year period, with the intent of obtaining regulatory approval for marketing Myloral. This study was a double-blind, placebo controlled clinical trial involving over 500 patients at ten U.S. and four Canadian medical centers.

6. Exhibit I is a graph illustrating the annual attack rate before and after treatment in the U.S. Phase III clinical trials of four multiple sclerosis drugs. Three of these drugs, Betaseron, Avonex, and Copaxone, have been approved for sale in the United States. The results depicted in the graph establish that the annual attack rate for multiple sclerosis patients who received Myloral in the AutoImmune Phase III clinical trial decreased substantially, as it did in the clinical trials of the three approved drugs. Thus, as shown by the results reported on Exhibit I, use of the Myloral composition resulted in approximately the same reduction in attack rate as each of the three drugs that have already been approved for commercial sale in the U.S. for treating multiple sclerosis.

7. The strong placebo effect shown in the Myloral study results, (as seen in Exhibit I) as compared with the other studies, is believed to be attributable to the fact that administration of Myloral to humans has no side effects, while administration to humans of each of the other three drugs results in side effects that are recognizable to the patient. For this reason, patients receiving placebo in the Myloral study had no basis upon which to ascertain whether they were receiving Myloral (or active agent) or placebo, while patients in the other studies to whom placebo was administered could often tell they were not receiving the active agent because they experienced few side effects. Thus, in the Phase III Myloral study the reduction in attacks resulting from the placebo effect was similar to the substantial reduction that resulted from bovine myelin administration.

8. Furthermore, patients who simultaneously received beta-interferon therapy had fewer attacks when treated with Myloral in comparison to placebo. The difference is shown in the attached graph (Exhibit II).

9. For these reasons, the clinical results of the Myloral Phase III study are consistent with the encouraging clinical results observed in the earlier limited clinical trial and with successful results obtained when administering myelin in the EAE animal model of multiple sclerosis.

10. Additional encouraging preliminary results were obtained in a study of

magnetic resonance imaging (MRI) data from the Phase III. Specifically, this study found an encouraging difference in "lesion load" for a genetic subgroup of patients treated with Myloral.

11. Consulting neurologists have informed AutoImmune Inc. that these findings are clinically meaningful and that further trials should be done.

12. I therefore disagree with the Examiner's statement that the Phase III trials demonstrate lack of efficacy. The substantial reduction in attacks experienced by patients taking Myloral is not an indicator of lack of efficacy, but is encouraging data. The MRI results are also encouraging.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11/18/97
DATE

DR. MALCOLM FLETCHER

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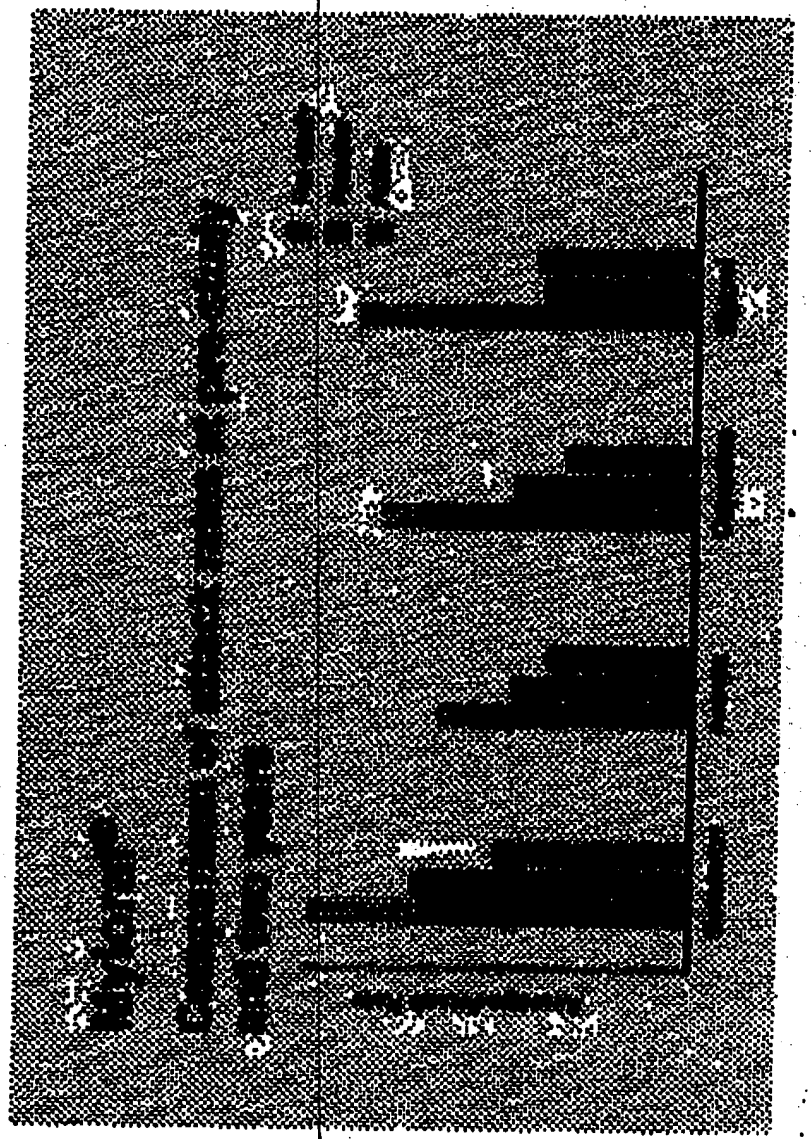


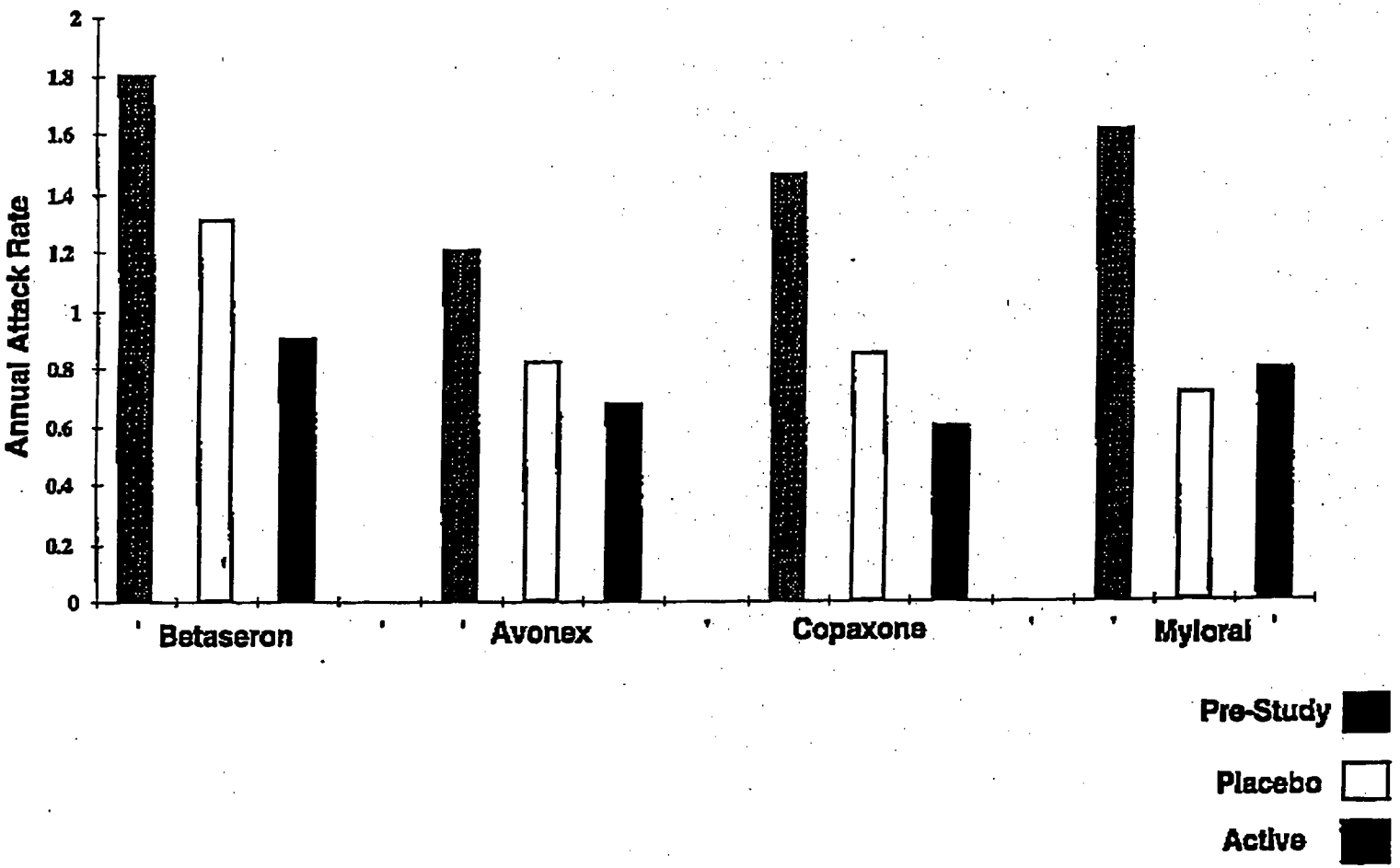
Exhibit I

Exhibit E

Concomitant β-Interferon Use

Exhibit I (second copy)

Attack Rates, Pre-Study & Two Years



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I hereby certify that this paper and every paper or fee referred to herein as being enclosed is being deposited with the U.S. Postal Service and that it was addressed for delivery to the Commissioner of Patents & Trademarks, Washington, DC 20231 by first class mail postage prepaid on APRIL 10, 1992 (date of deposit).

4.10.92
Date

Henrietta Mano
Signature

1010/06121
(ACG#46)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HOWARD L. WEINER ET AL.

Serial No.: 07/595,468 Examiner: B. Celsa

Filed: October 10, 1990 Group Art Unit: 1811

For: METHOD OF TREATING OR PREVENTING TYPE I DIABETES BY ORAL ADMINISTRATION OF INSULIN

Hon. Commissioner of
Patents & Trademarks
Washington, D.C. 20231

Date: March 16, 1992

considered 3/17/93 DMD.

DECLARATION OF GEORGE S. EISENBARTH

I, George S. Eisenbarth declare and state as follows:

1. I hold a Ph.D degree in Physiology-Pharmacology conferred by Duke University in 1974 as well as an M.D. degree conferred by the same institution in 1975. I am currently employed as Associate Professor, Department of Medicine by Harvard Medical School and I am also Head, Section of Immunology and Immunogenetics, Joslin Diabetes Center Boston, Mass. I have had extensive research and clinical experience in immunoendocrin-

ology and immunogenetics since 1979 particularly applied to diabetes. Type 1 diabetes, its autoimmune disease aspect, and pancreatic islet cells have been a main research interest of mine for at least 10 years. My activities in the field are reflected in more detail in the attached copy of my Curriculum Vitae (Tab 1).

2. I am a co-inventor of the patent application identified above and I have reviewed this application as well as the Office Action issued thereon on 12/10/91. I submit this declaration in rebuttal of the rejections of the application claims under 35 U.S.C. §101 and under 35 U.S.C. §112. It is my understanding that the Examiner considers the claims (copy attached - Tab 2) to be ambiguous in that, according to the Examiner, methods for identifying those genetically susceptible to Type 1 diabetes have not been perfected. It is also my understanding that the Examiner questions whether Type 1 diabetes is an autoimmune disease and whether the NOD model provides a good basis for extrapolating usefulness in humans of the claimed regime for treating or preventing human Type 1 diabetes. I also understand that the Examiner further questions whether tests involving insulin or insulin-derived peptides on the NOD model would be sufficient to establish activity of such substances for preventing or arresting autoimmune destruction of pancreatic beta cells in humans. I address all of these issues below.

The Autoimmune Nature of Type 1 Diabetes is Well-Established

3. Autoimmune disease is characterized by an immune response causing destruction of self tissue accompanied by specific inflammation of the target tissue. Precisely this type of destructive immune response takes place in Type 1 diabetes at an early stage: while pancreatic beta cells are still functioning. (After their complete destruction, the autoimmune character of the disease obviously ceases because there is no more target tissue for the immune system to attack.)

4. There is almost no longer a debate as to whether Type 1 diabetes is an autoimmune disease. A summary of the considerable evidence of the autoimmune nature of Type 1 can be found in Unger, R.H., et al, "Diabetes Mellitus" Williams Textbook of Endocrinology, 1991, Chapter 24 (Tab 3). This is the latest (8th) edition of a standard textbook. As stated on p.1262 of Tab 3, such evidence includes inter alia that:

- immunosuppression (of any type) prolongs beta cell function;
- autoimmune response (insulitis and specific beta cell destruction) resumes in individuals afflicted with Type 1 diabetes who have received beta cell transplants from identical twin siblings;
- presence of autoantisera (in fact, such presence is predictive of Type 1 diabetes);
- occurrence of the disease in families with this or other autoimmune disorders; and

- histologic evidence of tissue destruction.

5. The autoimmune nature of Type 1 diabetes is also accepted by the American Diabetes Association, Diabetes 39:1151-1152, 1990 - Tab 4. In Zhang, Z.J., et al, PNAS, 88:10252-10256, 1991 (Tab 5), of which I am a coauthor, we did not (at p. 10255) dispute the autoimmune nature of Type 1 diabetes. We merely said that it is unknown whether insulin is in fact an autoantigen for this disease, i.e. whether the hormone itself is the target of autoimmune attack.

Development of Type 1 Diabetes Can Be Predicted Years Before Hypoglycemia Occurs

6. The autoimmune destruction process can be detected very early during the long prodiemal phase of the disease by various well-known assays, including assays detecting islet cell antibodies, insulin autoantibodies, as well as intravenous glucose tolerance tests. See, e.g., Eisenbarth, G.S. "Type 1 Diabetes Mellitus: A Chronic and Predictable Autoimmune Disease," in Current Concepts, The Upjohn Company, 1989 especially pp. 5-8 and pp. 19-20 (Tab 6). See, also, Ziegler, A.G., et al, Diabetes Care, 13:762-775 (copy not attached but previously submitted to the Examiner). The aforementioned assays are not concerned with the genetic susceptibility aspects of the disease, although genetic susceptibility can also be detected in essentially all cases. (See Tab 4 and Tab 6.)

7. Measured with current methodology (combining measurement of autoantibodies and metabolic function), between 90 and 100% of high-risk diabetic relatives develop the disease within 5

years. However, 100% accurate prediction of individuals that will develop Type 1 diabetes is not necessary prior to the present oral (or by-inhalation) tolerization process. Insulin thus administered breaks down in the gut and has no metabolic effect. Thus, there is no danger of hypoglycemia (and certainly not of ketoacidosis, which is never caused by insulin). The absence of metabolic effect is precisely the reason that attempts to deliver insulin orally to patients with overt Type 1 diabetes have been considered ineffective. See, Zhang, et al., supra, at 10253, and Example 2 of the present application. Furthermore, insulin orally administered to patients with overt Type 1 diabetes can have little tolerizing effect because these patients have few, if any, beta cells remaining and with time present no signs of autoimmune inflammation, i.e., (after one year of overt diabetes) these patients present no insulitis, which is a characteristic symptom of Type 1 diabetes during the autoimmune phase. (Gepts, W., "Pancreatic Pathology of Juvenile Diabetes Mellitus," in Secondary Diabetes: The Spectrum of the Diabetic Syndromes, Podolsky, S., et al., eds., Raven Press, N.Y., 1980, pp. 15-32 - Tab 8.) Thus, it is not necessary for the present invention to provide "perfect" methods of identifying susceptible individuals. Nevertheless, as the above-cited publications show, excellent screening methods exist at the prodromal stage of the disease. Genetic analysis can add to the prediction of diabetes (e.g., HLA alleles DR3 and DR4) by identifying individuals to be screened for autoantibodies and metabolic function (Tab 6).

Reliability of the NOD Model

8. The NOD mouse model has become the most important and relevant animal model for Type 1 diabetes, especially for the autoimmune aspects of Type 1. The NOD model is very similar to human Type 1 diabetes. Similarities include an identical amino acid mutation of the NOD class II allele (lack of Asp at position 57 of the mouse I-A or of the human DQ gene) which is essential for susceptibility to the disease. NOD mice develop diabetes that not only involves beta cell destruction (as does human Type 1) but is also accompanied by insulitis (inflammation of Langerhan's islet cells) which in humans is so closely associated with Type 1 diabetes as to constitute a recognized hallmark of the autoimmune phase of the disease. (Foulis, A.K., et al., Diabetologia, 1986, 29:267-274.)

9. Further similarities between the NOD model and human Type 1 diabetes are outlined in Williams, supra, Chapter 31 (especially at pp. 1560-1561) which I have coauthored with Dr. Richard A. Jackson (Tab 7).

10. Naturally, no animal model should ever be considered identical to any human disease, but models are extremely useful in screening pharmacological agents. The NOD mouse is the best model of Type 1 diabetes available. It is used in research for immune therapies of the disease. I myself use extensively and exclusively this model and have done so for at least 7 years. In addition, the reliability of this model is strengthened by the fact that known therapies (including an immune suppressive

approach) effective in man are also effective in the NOD and vice versa: Metabolic insulin therapy (which is standard therapy in overt Type 1 diabetes) is effective in the NOD as is the (nonspecific) immunosuppressant Cyclosporin A (which was tried in the NOD mouse prior to human trials). Cyclosporin A has also been effective in man, although it is of limited usefulness precisely because it is not specific.

11. In the case of oral tolerization against autoimmune diseases in general, mouse models have predicted accurately efficacy of oral tolerization of humans. (See, Weiner declaration.) The mechanism of oral specific tolerization (or tolerization by inhalation) appears to be the same in mouse and man. (Id.)

12. Based on the facts and conclusions set forth in Paragraphs 8-11 above, Dr. Richard A. Jackson (my colleague and co-author of Tab 7) and myself are planning to conduct a human clinical study involving 2 normal controls to be followed by a trial administration of oral insulin in 10 children with active autoimmune destruction of beta cells. The study will commence in 1992 under the auspices of The Joslin Diabetes Center.

Neither I as a physician and scientist, nor in my opinion and experience the Center's Institutional Review Board, would undertake such a study unless we believed that the treatment would be successful. We formed this belief based on the studies of oral insulin in NOD mice and our ability to predict diabetes.

Ascertaining Whether an Insulin Fragment Suppresses Autoimmune Destruction

13. Based on the contents of Paragraphs 8-11, I conclude that the NOD model provides a convenient and reliable assay for testing whether a particular insulin-derived peptide suppresses autoimmune response directed against beta cells. All a person of ordinary skill in the field has to do is duplicate the assay of Example 1.

Alternatively, insulitis can be used to determine the extent of autoimmune response since it accompanies diabetes (in both NOD mice and humans). Insulitis is determined by a well-known method involving simple "scoring" of Langerhan's islet cells by histologic examination. (See Weiner declaration.)

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the present application or any patent issuing thereon.

3/26/92
Date

George S. Eisenbarth

(ACG#46:06121EIS.DEC)